CLAIMS

That which is claimed is:

1. An array comprising a plurality of modified oligonucleotide compositions stably associated with the surface of a support, wherein each oligonucleotide composition is characterized by:

an oligonucleotide backbone structure modified from that of a naturally occurring nucleotide polymer;

wherein the oligonucleotides of the composition are characterized by a binding affinity greater than that of a corresponding, non-modified oligonucleotide.

2. The array of claim 1, wherein the oligonucleotides are comprised of a modification at the 2' site of the sugar group of at least one nucleotide.

3. The array of claim 1, wherein the oligonucleotides are comprised of at least one modified internucleoside linkage.

4. The array of claim 1, wherein said modified oligonucleotides have an average length of from about 80 to about 300 nucleotides.

5. The array of claim 1, wherein said modified oligonucleotides have an average length of from about 100 to about 200 nucleotides.

6. The array of claim 1, wherein oligonucleotides of each of said oligonucleotide compositions has a different sequence from oligonucleotides of any other oligonucleotide composition on the array.

7. The array of claim 1, wherein each oligonucleotide composition comprises a population of identical oligonucleotides.

8. The array of claim 1, wherein each oligonucleotide composition comprises a plurality of oligonucleotides that bind to a particular nucleic acid.

9. The array of claim 1, wherein the number of oligonucleotide compositions on said array ranges from about 2 to about 10^9.

10. An array comprising a plurality of modified oligonucleotide compositions stably associated with the surface of a support, wherein each oligonucleotide composition is characterized by:

an oligonucleotide backbone structure modified from that of a naturally occurring nucleotide polymer;

wherein the oligonucleotides of the composition is characterized by a pH stability of at least one hour at 37°C at a pH in a range of about 0.5 to about 10.

11. The array of claim 10, further comprising a blocking chemical modification at or near at least one end of said oligonucleotide, wherein the oligonucleotide is further characterized by having a nuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same sequence and number of bases.

12. The array of claim 10, wherein the oligonucleotide is stable at a pH of from 0.5 to 6.0.

13. The array of claim 10, wherein the modified oligonucleotide is further characterized by modification of at least 25% of the internucleoside linkages of the oligonucleotide.

14. An array comprising a plurality of oligonucleotide compositions stably associated with the surface of a support, wherein each oligonucleotide composition is characterized by:

an oligonucleotide backbone structure modified from that of a naturally occurring nucleotide polymer; and

a blocking chemical modification at or near at least one end of the oligonucleotide;

wherein the oligonucleotide is characterized by a nuclease resistance of at least twice that of a naturally occurring polymer having the same number of nucleotides.

15. An array of modified oligonucleotides, the array comprising:

a planar, non-porous solid support having a surface;

a plurality of different modified oligonucleotides attached to the surface of the solid support at a density exceeding 400 different modified oligonucleotides/cm^2,

wherein each of the different modified oligonucleotides is attached to the surface of the solid support in a different predefined region, has a different determinable sequence, and is at least 80 nucleotides in length; and

further wherein the modified oligonucleotides are characterized by a characteristic selected from the group consisting of (a) a binding affinity of at least about 1.25 times that of a corresponding, non-modified oligonucleotide, (b) a pH stability of at least one hour at 37°C at a pH in a range of about 0.5 to 10; and (c) a nuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same sequence and number of bases.

16. A method of analyzing comprising the steps of:

(a) contacting a first sample of naturally occurring nucleic acid sequences with an array comprised of a solid support sequence having bound to its surface a plurality of modified nucleic acid sequences;

(b) allowing sequences of the sample to hybridize to the modified sequence of the array;

(c) analyzing results of the hybridizing;

(d) removing sequences hybridized to sequences of the array using a removing agent selected from the group consisting of a solution having a pH of less than 6.0 and a nuclease which enzymatically destroys natural nucleic acid sequences; and

(e) repeating (a), (b), (c) and (d) with a second sample of naturally occurring nucleic acid sequences.

17. The method of claim 16, wherein (a), (b), (c) and (d) are repeated a plurality of times with different samples of naturally occurring nucleic acid sequences.

18. A method for detecting nucleic acid sequences in two or more collections of nucleic acid molecules, the method comprising:

(a) providing an array of modified polynucleotides bound to a solid surface, each said modified polynucleotide comprising a determinable nucleic acid;

(b) contacting the array of modified polynucleotides with:

(i) a first collection of labeled nucleic acid comprising a sequence substantially complementary to a nucleic acid of said array, and

(ii) at least a second collection of labeled nucleic acid comprising a sequence substantially complementary to a modified polynucleotide of said array;

wherein the first and second labels are distinguishable from each other; and

(c) detecting hybridization of the first and second labeled complementary nucleic acids to nucleic acids of said arrays;

wherein the modified oligonucleotides are characterized by a characteristic selected from the group consisting of (a) a binding affinity of at least about 1.25 times that of a corresponding, non-modified oligonucleotide, (b) a pH stability of at least one hour at 37°C at a pH in a range of about 0.5 to 10; and (c) a nuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same sequence and number of bases.

19. A method of using a label to detect hybridization with modified polynucleotide probes of known sequence, said method comprising:

(a) contacting under hybridization conditions a labeled polynucleotide sequence with a collection of modified polynucleotide probes of known sequences wherein said probes are attached to a substrate at known locations; and

(b) determining the sequences of the probes which hybridize with the labeled polynucleotide, said collection comprising at least 100 different probes per square centimeter of substrate.

20. A method of identifying nucleotide differences between the sequence of a target nucleic acid and the sequence of a reference nucleic acid comprising:

a) providing a substrate having at least 1000 different modified polynucleotide probes of known sequence at known locations, attached at a density of at least 10,000 probes per square cm;

b) contacting the target nucleic acid with the modified polynucleotide probes attached to the substrate under conditions for high specificity complementary hybridization;

c) determining which modified polynucleotide probes have hybridized with the target nucleic acid; and

d) using a computer to (i) compare the sequence of the reference nucleic acid with the sequences of the modified polynucleotide probes that have hybridized with the target nucleic

acid and (ii) identify the nucleotide differences between the sequence of the target nucleic acid and the sequence of the reference nucleic acid.

21. A method for synthesizing modified oligonucleotides on a solid phase comprising the steps of:

(a) loading an aqueous solution of a selected modified oligonucleotide in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus,

(b) tapping the tip of the dispensing device against a solid support at a defined position on the surface, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface, and

(c) repeating steps (a) and (b) plurality of times.

add A1 add B1